行政院國家科學委員會專題研究計畫成果報告
Nalbuphine 前驅藥長效植入劑藥動學及藥效學之研究

計畫編號：NSC-2314-B-041-007
執行期限：87 年 8 月 1 日至 88 年 7 月 31 日
主持人：宋國峻　執行單位：嘉南藥理學院藥學系

Abstract

The major purpose of this project is to develop and evaluate a series of prolong-released implantable microspheres loaded with various nalbuphine prodrugs. Three major studies were included in this project: the in vitro drug release study, in vivo pharmacokinetic study and in vivo pharmacodynamic study. The results indicate that higher in vitro and in vivo drug release rates were observed for the microspheres loaded with more hydrophilic prodrugs. The rabbit paw pressure experiments also indicate that the microspheres loaded with more hydrophilic prodrug had higher percent analgesic effect. The results suggest the different physicochemical properties of nalbuphine prodrugs may attribute to the various in vitro/in vivo release rates from microspheres and therefore affect their pharmacodynamic performance.

Keywords: Nalbuphine prodrug, Prolong-released microsphere, Drug release, Pharmacodynamics

中文摘要

本計畫主要目的在於評估一系列新開發之 Nalbuphine 前驅藥長效植入微球粒劑型其生體外、生體內藥物釋放速率及其藥效學之研究。於生體外及生體內之藥物釋放結果顯示不同親水性之前驅藥對藥物釋放動力學有所影響；當前驅藥親水性增加時，藥品於生體外及生體內之釋放速率皆上升，顯示其生體內藥物釋放速率可由生體外之藥物釋放所反映出來。利用兔隻壓掌實驗可得知生體內藥物釋放快且完全的藥物其止痛效果也較佳。因而對此系列 Nalbuphine 前驅藥長效植入微球粒劑型而言，其藥品之物化性質--生體外/生體內藥物釋放速率--生體內藥效間有相當好的相關性。

關鍵詞：Nalbuphine 前驅藥，長效植入微球粒劑，藥物釋放，藥效學

Introduction

Nalbuphine is a narcotic analgesics which is often used in the treatment of both acute and chronic pain [1,2]. It is a potent analgesics with relatively low side effects. Owing to its short elimination half-life and low oral bioavailability, frequent injections are needed. It is obvious that patient compliance and therapeutic effectiveness may be improved by maintaining the plasma nalbuphine concentration. As a result, a series of nalbuphine prodrugs with various hydrophilicities have been synthesized, including nalbuphine propionate, nalbuphine pivalate and nalbuphine decanoate. Various nalbuphine prodrug formulations such as biodegradable implant, suspension and microsphere have also been developed[3,4].

The major purpose of this project is to study the pharmacokinetics and pharmacodynamics of nalbuphine prodrugs released from implantable microspheres. This basic research may help to understand the *in vivo* performance of the microspheres and it may eventually lead to develop nalbuphine prodrug implantable microspheres to decrease the injection frequency and to improve the therapeutic quality for severe pain patients.

Results and discussion

Preparation of drug loaded microsphere

Nalbuphine prodrug loaded microspheres were prepared by the emulsion-solvent evaporation process. The 2% drug and 2% polymer were dissolved in methylene chloride and drop in aqueous phase contain 7mM SLS and 1M NaCl. The microdroplets were then solidified by the slow evaporation of the organic solvent with ice bath.

The nalbuphine prodrugs used in the present study were nalbuphine propionate, nalbuphine pivalate and nalbuphine decanoate; the biodegradable polymer used was poly-(lactide).Under the examination of SEM, these microspheres looked spherical and fairly uniform in size. The diameter of the microspheres was approximately 25 μm. The drug loading percentages were 23.0%, 30.1% and 25.7% for those various prodrug loaded microspheres, respectively.

In vitro release study

The influence of prodrug hydrophilicity on drug release from microspheres is shown in Figure 1. A greater drug release was observed for the microspheres loaded with the more hydrophilic prodrug. For example, after 48 hours, around 44.7%, 36.3% and 18.3% of nalbuphine propionate, nalbuphine pivalate and nalbuphine decanoate have released from the microspheres, respectively.

In vivo pharmacokinetic study

To study the pharmacokinetics and pharmacodynamics of the prodrugs released from microspheres, the New Zealand rabbits was used as an animal model. The implantable microspheres was injected into rabbits and plasma drug concentrations will be monitored using a HPLC method [5].

Figure 2 shows the in vivo plasma concentration vs time profiles for the various nalbuphine prodrugs released from microspheres. The nalbuphine prodrugs can be hydrolyzed by esterase in a short time, as a result, the Y-axis in the Figure 2 represent the concentration of nalbuphine (the parent drug). Figure 2 shows that, a slightly faster release and higher AUC can be observed for microsphere loaded with nalbuphine propionate relative to nalbuphine pivalate. A much slower drug release can be observed for the microsphere loaded with nalbuphine decanoate. These results correlate well with the in vitro results and suggest that the prodrug hydrophilicity may also affect the in vivo drug release from the microspheres.

Pharmacodynamic study

A rabbit paw pressure model were used in this study to monitor the pharmacodynamic response of rabbits. Figure 3 shows the percent analgesic effect vs time profiles for the various prodrug loaded microspheres. A higher analgesic effect were observed for microspheres loaded with more hydrophilic prodrugs. The results were similar to the concentration-time profiles in the Figure 2. Accordingly, from Figure 1, Figure 2 as well as Figure 3, the results show a correlation among the physicochemical properties of the prodrugs, the in vitro/in vivo release profiles and the pharmacological response; that is, the results suggest the different physico-chemical properties of nalbuphine prodrugs may attribute to the various in vitro/in vivo release rates from microspheres and therefore affect their pharmacodynamic performance.

Comments

Most of the content in this study are in accordance with the proposal, although some changes exists due to evolution of this project. This study has been written in a paper format and prepared to be sent for publication in a scientific journal.

References

1. W.K.Schmidt, S.W.Tam, G.S. Schotzberger, D. H. J. Smith, R. Clark and V. G. Vernier, *Drug Alcohol. Depend.*, 14 (1985) 339.

2. G.C.Pugh and G.B.Drummond, *Br. J. Anesth*, 59 (1987) 1356.

3. K. C. Sung, R. Y. Han, O. Y. P. Hu and L. R. Hsu (1998), *Intern. J. Pharm.*, 172: 17-25.
4. J. Wang, (1992), Ph. D. Dissertation: *Pharmacodynamic and Pharmacokinetic Studies with Long-acting Novel Nalbuphine Prodrugs.*
5. Ho, S. T., Wang, J. J., Hu, O. Y. P., Chiang, P. S. and Lee, S. C., *J. Chromatogr.*, B 678 (1996) 289-296.

Figure 1. In vitro percent released vs time profiles of nalbuphine prodrugs from microspheres

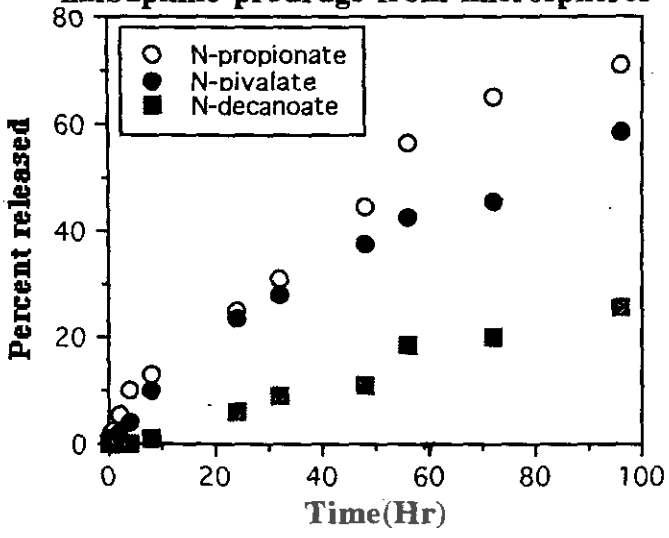

Figure 2. In vivo plasma concentration vs time profiles for nalbuphine prodrugs from microspheres

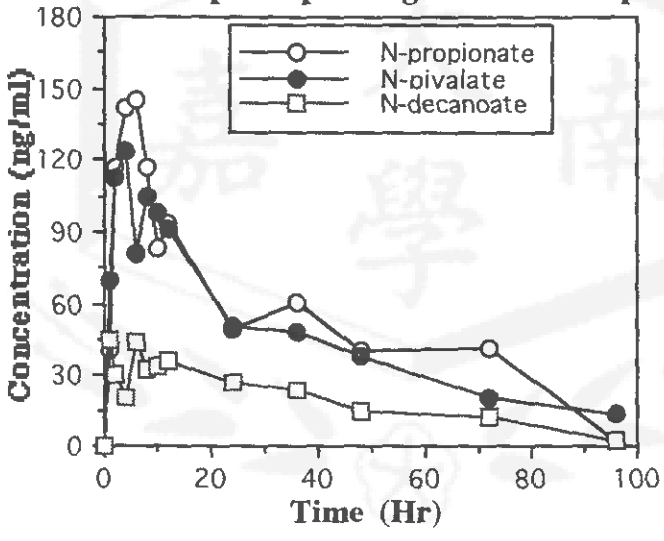

Figure 3. Percent analgesic effect vs time profiles for nalbuphine prodrugs from microspheres